POST TRANSPLANTATION HYPERTENSION

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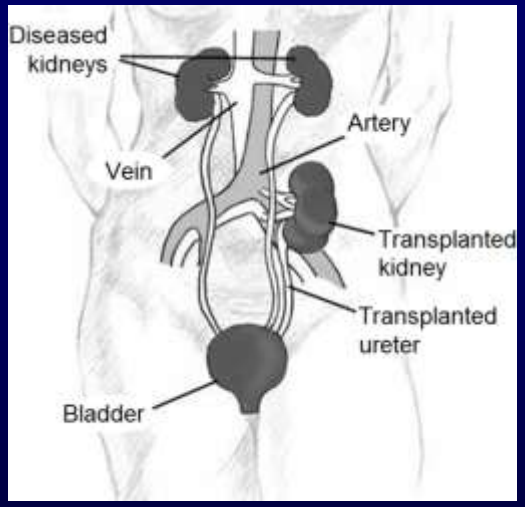
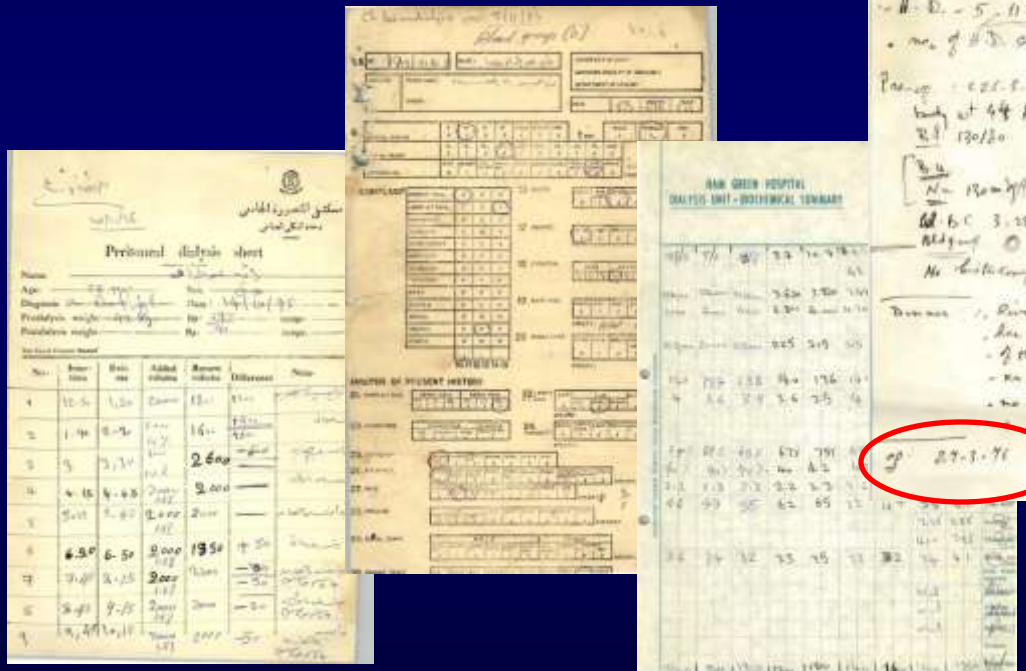
TRANSPLANTATION HISTORY

- **First Transplanted Patient in Mansoura 27 Mar 1976**

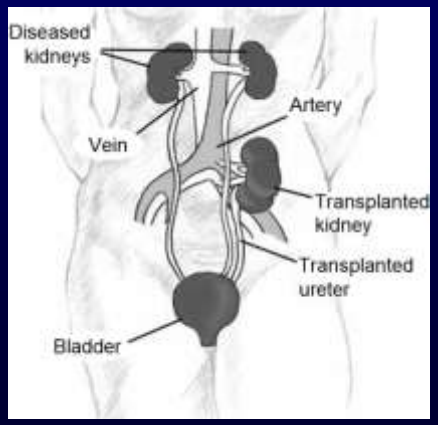




CURRENT

- **2600 living donor transplant recipients [100 per year].**

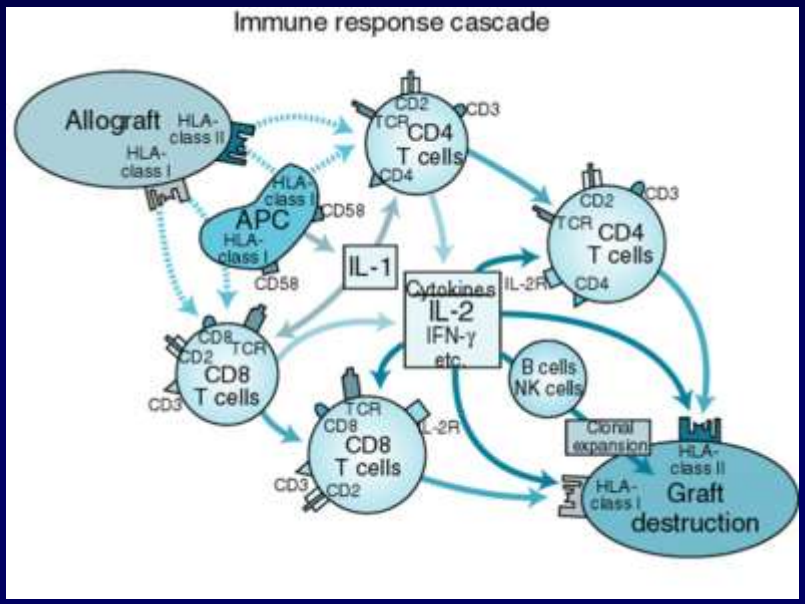
Transplantation



Kidney graft perfusion

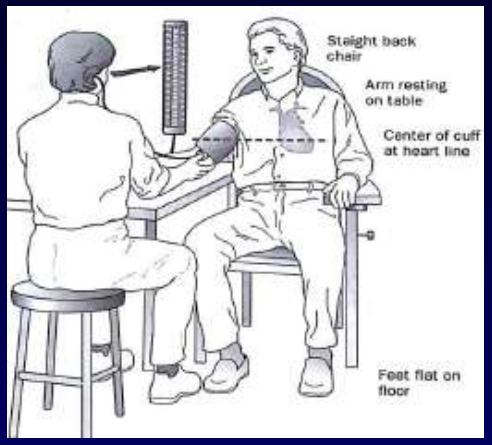
Donor nephrectomy

TRANSPLANTATION



SURGERY **IMMUNOSUPPRESSION**

Introduction



Arterial hypertension:

- **Is common in renal transplantation.**
- **Plays a major role in the progression to chronic allograft failure and in the morbidity and mortality associated with cardiovascular disease.**
- **With each increment of 20/10 mm Hg, the risk for CVD doubles.**
- **The benefits of sustained lowering of the BP are:**
  1) **35% to 40% reduction in the incidence stroke.**
  2) **20% to 25% reduction in the incidence of acute myocardial infraction.**
  3) **50% reduction in the incidence of congestive heart failure.**

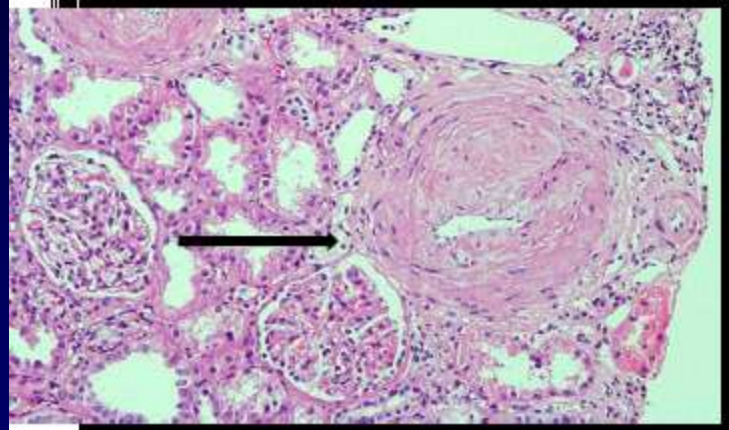
Hypertension After Kidney Transplantation

- Introduction
- **Prevelance**
- Risk Factors, causes of HTN
- Impact on graft & Patient survival
- HTN & Cardiovascular disease
- Diagnosis of Post Tx-HTN
- Management

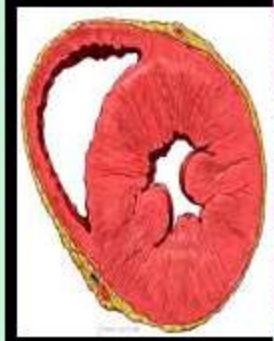
Prevalence

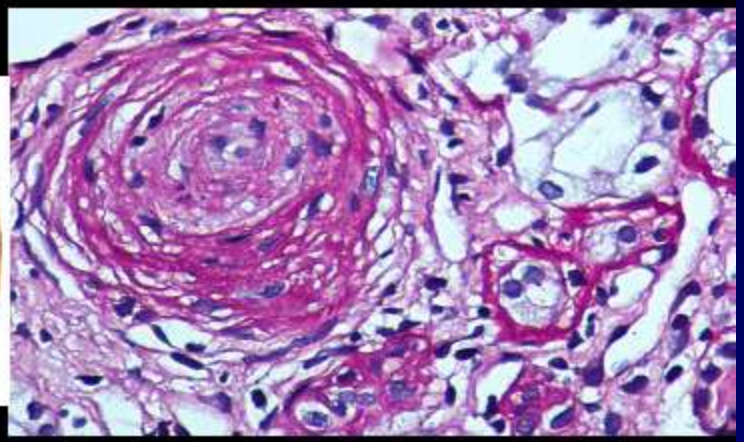
- Varies with the type of immunosuppressive regimen, time after transplantation.
- Increased from 30% to 40% in the precyclosporine (CyA) era to 75% to 90% after the introduction of CyA.
- Associated with a graded increase of subsequent graft failure.

Renal transplant biopsy- HTN

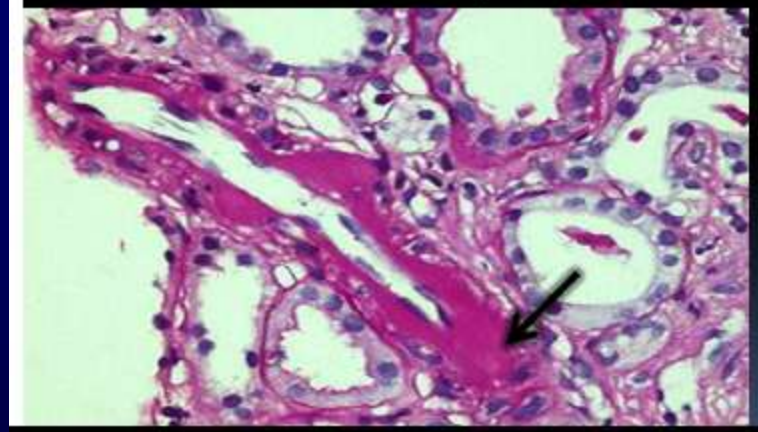


Markedly thickened blood vessels with narrow slit like lumen. H&E , X100

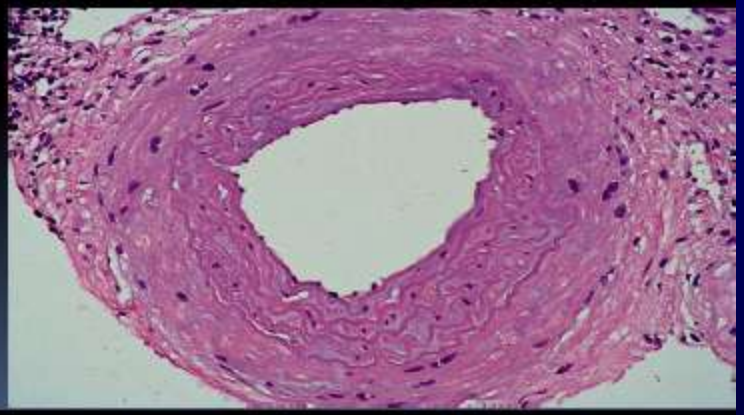




Malignant hypertension. Hyperplastic arteriolosclerosis with concentric intimal thickening by mucoid ground substance and loosely arranged connective tissue fibres. PAS, X200



Benign nephrosclerosis. Note the thickening of the arteriolar wall by hyaline material accumulating under the endothelium. PAS, X200



Benign nephrosclerosis.Marked intimal fibrosis , luminal narrowing and duplication of the internal elastic lamina. H&E X200

Causes of Posttransplant Hypertension

Recipient related

Pre-existing hypertension and LVH

Body mass index

Primary kidney disease (native kidneys)

Donor related

Elderly and female donor

Hypertensive donor

Use of right-sided donor kidney

Transplantation related

Prolonged ischemia time

Delayed graft function

Immunosuppressive therapy

Calcineurin inhibitors (CyA and TAC)

Corticosteroids

Renal transplant artery stenosis

Renal outflow obstruction (lymphocele, ureteral stenosis)

Renal transplant dysfunction (CAN, GN)

Abbreviations: CAN, chronic allograft nephropathy; GN, glomerulonephritis

POST TRANSPLANTATION HYPERTENSION

CAUSES:

RENOVASCULAR

- GRAFT ARTERY STENOSIS
- VASCULAR REJECTION

PARENCHYMAL

- REJECTION:
  - ACUTE CELLULAR
  - AB MEDIATED
  - CHRONIC ALLOGRAFT NEPHROPATHY
- MEDICATIONS:
  - CALCINEURIN INHIBITORS
  - STEROIDS
- Renal Dysfunction
- Native Kidneys
- Essential Hypertension

Hypertension After Kidney Transplantation

- Introduction
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- **Risk Factors, causes of HTN**
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Risk Factors Associated with Post-transplantation Hypertension

(A) *Pérez Fontán et al. 1999* (680 patients)

- At 1 year after transplantation:
  - (a) Pretransplant BP level.
  - (b) Grafting of the right kidney.
  - (c) Delayed graft function (DGF).
  - (d) Cold and warm ischemia.
  - (e) Transplantation from an elderly or female donor.

(B) *Kasiske BL et al, 2004* (1,600 patients)

- Factors such as male sex, recipient age, BMI, acute rejection (AR), lower hemoglobin levels, administration of CyA, and higher doses of prednisone were predisposing to hypertension.

CYCLOSPORIN (CyA) VS TACROLIMUS (TAC):

- Decreased effective renal plasma flow, glomerular filtration rate, and renal blood flow in CSA group.
- ↑ renal vascular resistance during CyA administration.
- TAC → better graft function & less risk of hypertension.

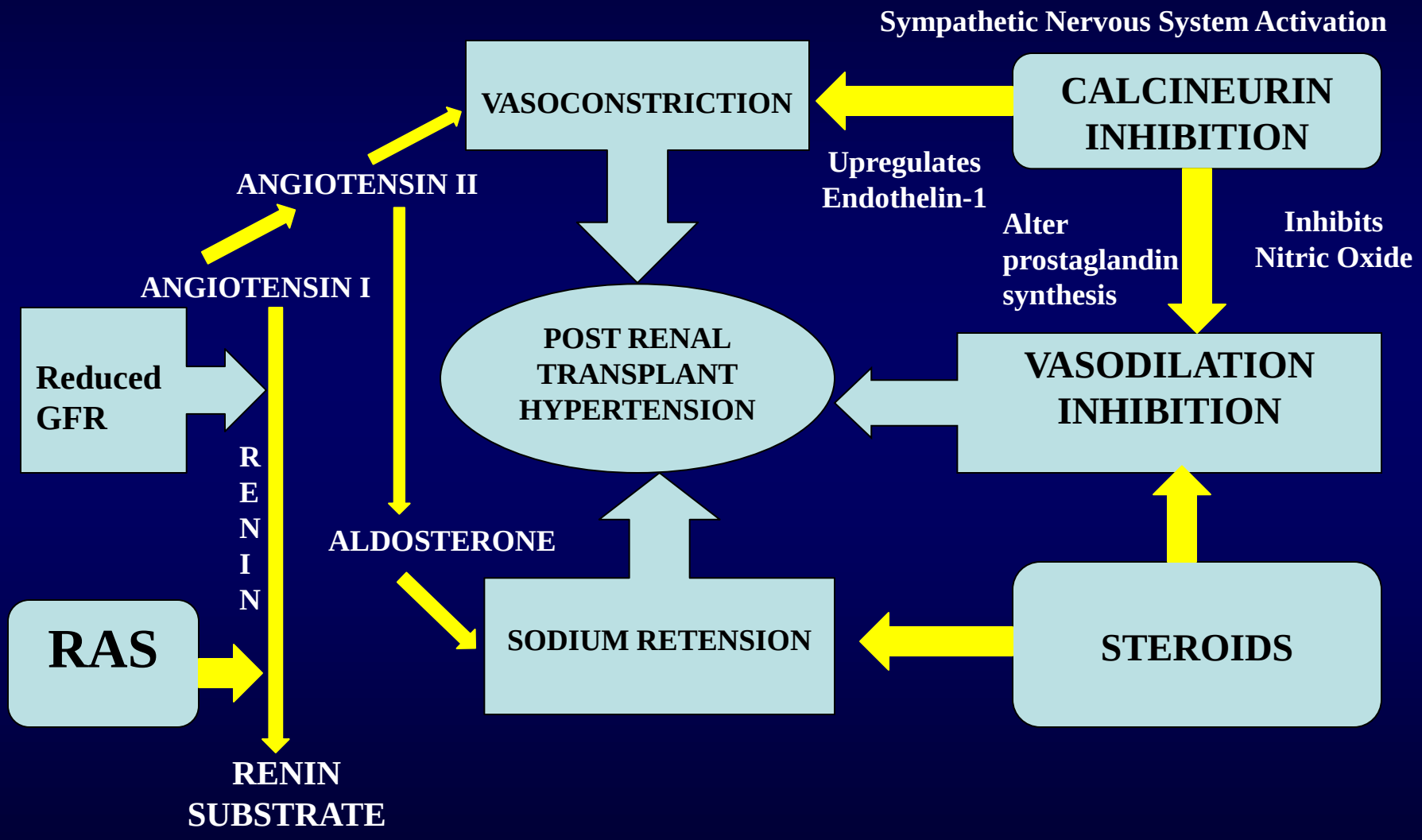
Klein et al., 2002

- TAC is associated with reduced requirement for antihypertensive therapy at 5 yrs follow up.

Vincenti et al., 2002

- Switching from CyA → TAC showed an improvement in BP as measured by ambulatory blood pressure monitoring (ABPM). *Ligtenberg et al., 2001*

The mechanism of CNI & STEROIDS-induced Hypertension



Mangray et al, Am J Kidney Dis. 2011;57(2):331-341

Acute Rejection

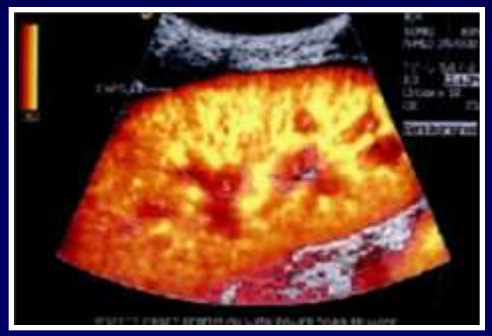
- A significant correlation between HTN posttransplant and risk for AR; independent of graft function was found.
- AR was associated with higher levels of systolic BP and/or diastolic BP posttransplant. Higher BP levels also were associated with earlier episodes of AR.
- Multivariable analysis → AR was associated significantly with systolic BP (↑ B.P. may antedate AR by even 3 ws).
- ↑ BL.P. is ass. with acute rejection (81% versus 22%).

(Cosio et al., 2001)

Power Doppler Sonography in Early Renal Transplantation: Does It Differentiate Acute Graft Rejection from Acute Tubular Necrosis?

Haytham M. Shebel[1], Ahmed Akl[2], Ahmed Dawood[1], Tarek A. El-Diasty[1], Ahmed A. Shokeir[3], Mohamed A. Ghoneim[3]

BORDERLINE REJECTION



ACUTE REJECTION (GI/II)

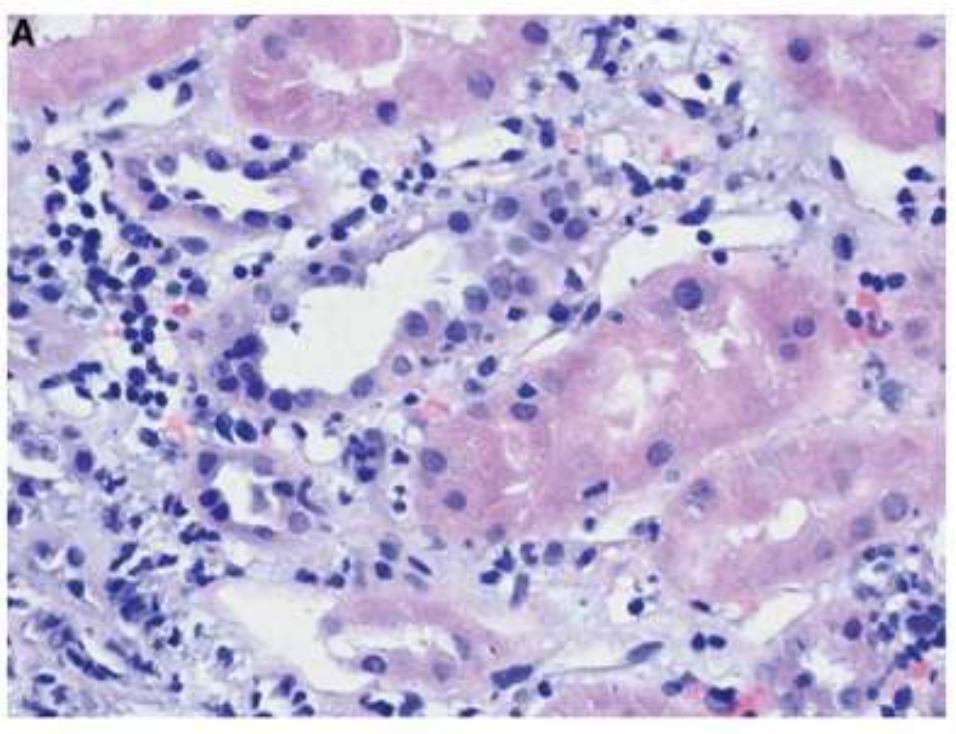
ACUTE REJECTION (GIII)

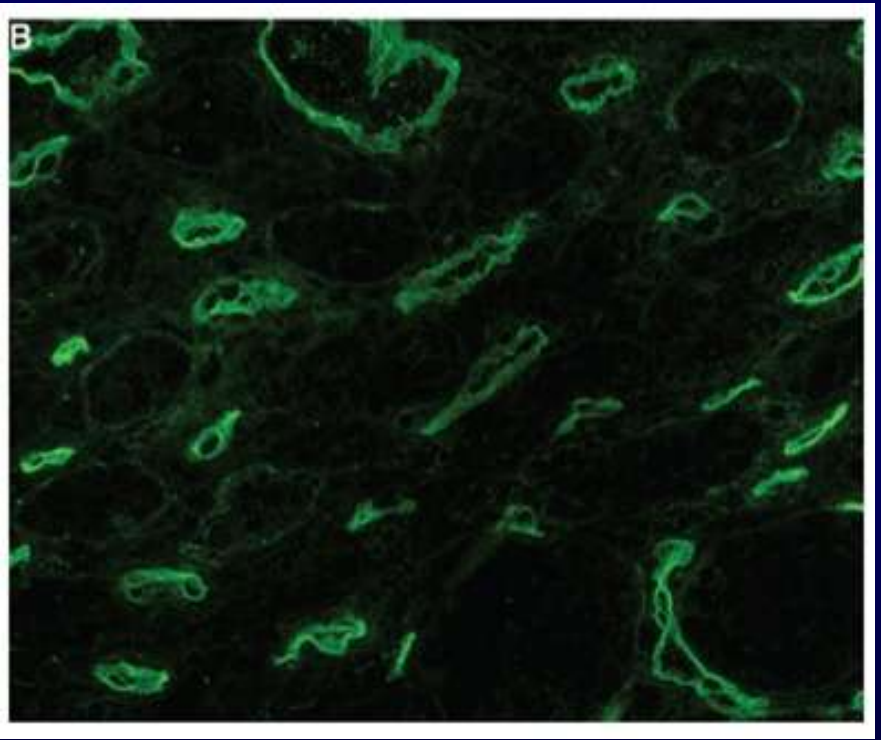
ATN

CT ANGIOGRAPHY

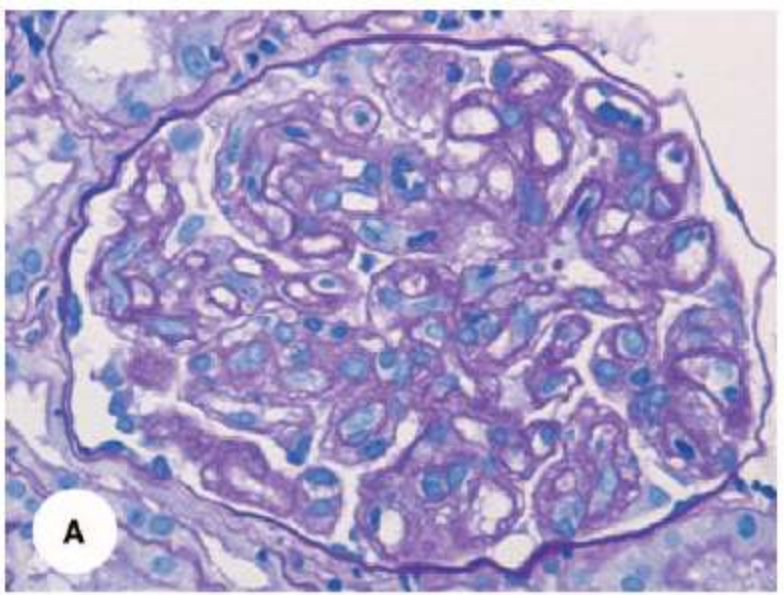
Kidney graft biopsy

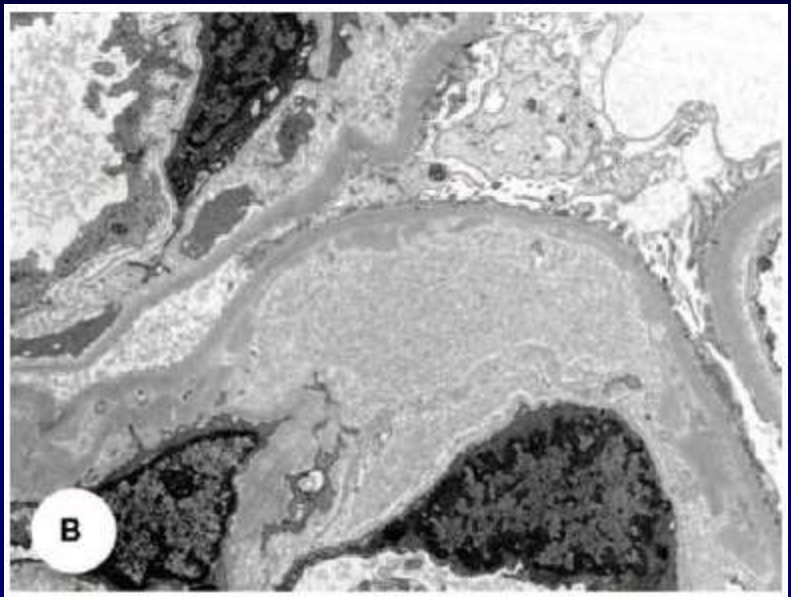
Acute rejection

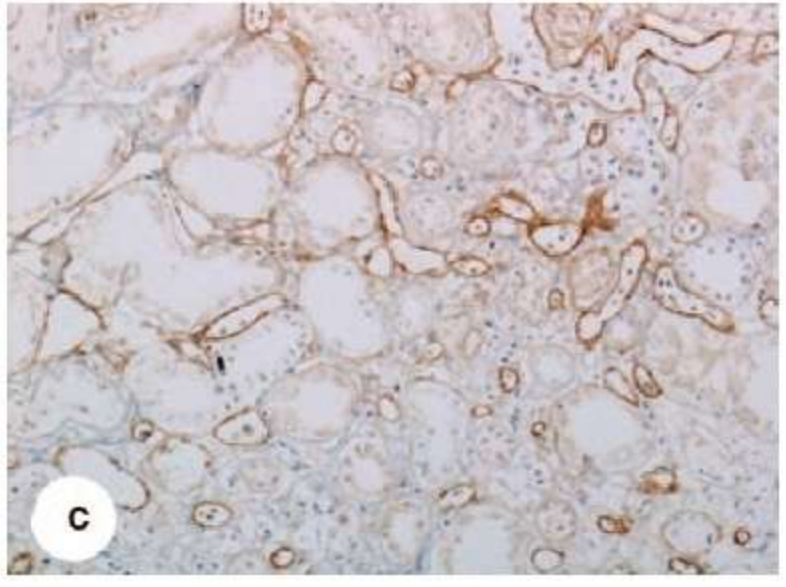




Transplant glomerulopathy







(A) Light microscopy of transplant glomerulopathy (TGP) showing numerous glomerular capillary walls with double contours enclosing a clear to flocculent region. (B) Electron microscopy of TGP showing widening of the subendothelial aspect of capillary walls by pale to flocculent proteinaceous material and one or more lamella of basement membrane material beneath the endothelial cell lining. One capillary also contains cell interposition between the basement membrane and endothelium. (C) C4d in chronic allograft showing area of

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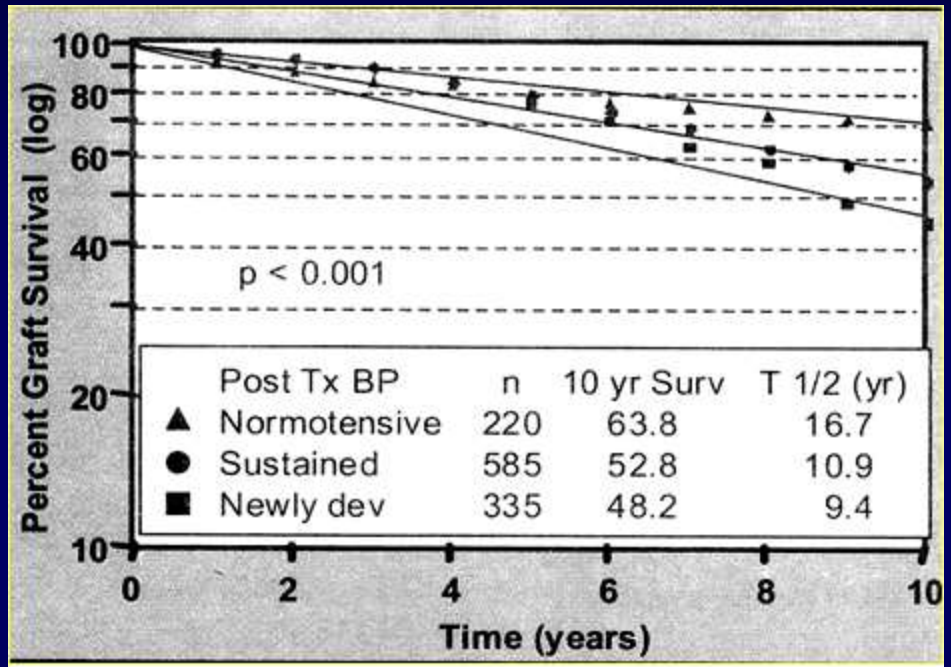
Impact of Hypertension on Graft Survival



Live-Donor Renal Transplantation at the Urology & Nephrology Center of Mansoura: 1976-1998

Mohamed A. Ghoneim, Mohamed A. Bakr, Nabil Hassan, Ihab Wahba, Ashraf S. Fouda, Mohamed A. Sobh, Ahmed B. Shehab El-Dein, Ahmed A. Shokeir, Mohsen M. El-Mekresh, Bedair Ali-El-Dein, Yasser M. Osman, Amani Moustafa, Farha El-Chenawi

Department of Urology, Division of Nephrology and Division of Clinical Immunology, The Urology & Nephrology Center, Mansoura, Egypt

Clinical Transplants 2001, Cecka and Terasaki, Eds. UCLA Immunogenetics Center, Los Angeles, California

Impact of Hypertension on Graft Survival

Graft survival relative to posttransplantation variables.

	No. of patients	5-year survival %	95% CI		10-year survival %	95% CI		*P* value (log rank)
Post-transplant hypertension								
(i) Normotensive	758	86.2	83.46	88.94	75.7	71.58	79.82	
(ii) Sustained hypertension	809	88.0	85.65	90.45	65.9	62.18	69.62	**<0.001**
(iii) Newly developed hypertension	400	85.7	82.17	89.23	56.0	50.71	61.29	

Research Article

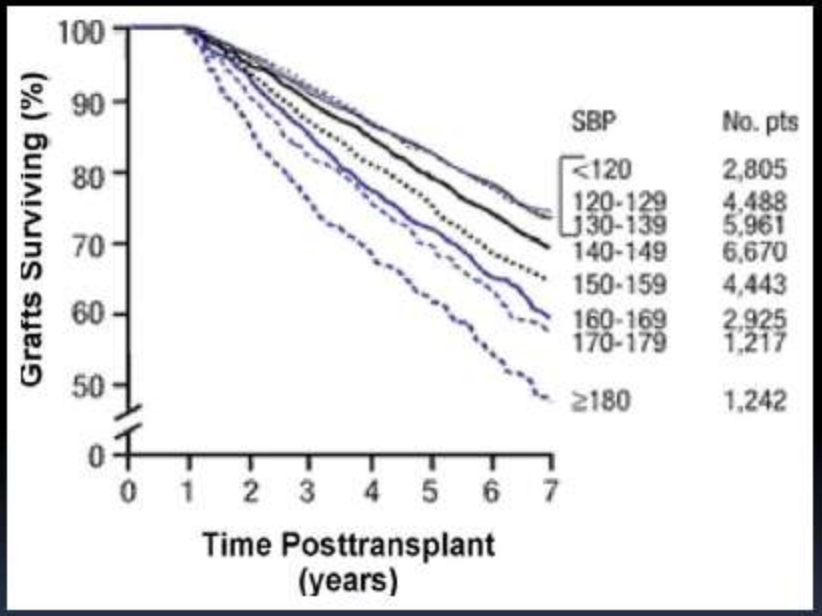
Factors Affecting Graft Survival among Patients Receiving Kidneys from Live Donors: A Single-Center Experience

Mohamed A. Ghoneim,[1] Mohamed A. Bakr,[2] Ayman F. Refaie,[2] Ahmed I. Akl,[2] Ahmed A. Shokeir,[1] Ahmed B. Shehab El-Dein,[1] Hesham M. Ammar,[2] Amani M. Ismail,[3] Hussein A. Sheashaa,[2] and Mahmoud A. El-Baz[4]

[1] *Department of Urology, The Urology & Nephrology Center, Mansoura, Egypt*
[2] *Division of Nephrology, The Urology & Nephrology Center, Mansoura, Egypt*
[3] *Division of Immunology, The Urology & Nephrology Center, Mansoura, Egypt*
[4] *Division of Pathology, The Urology & Nephrology Center, Mansoura, Egypt*

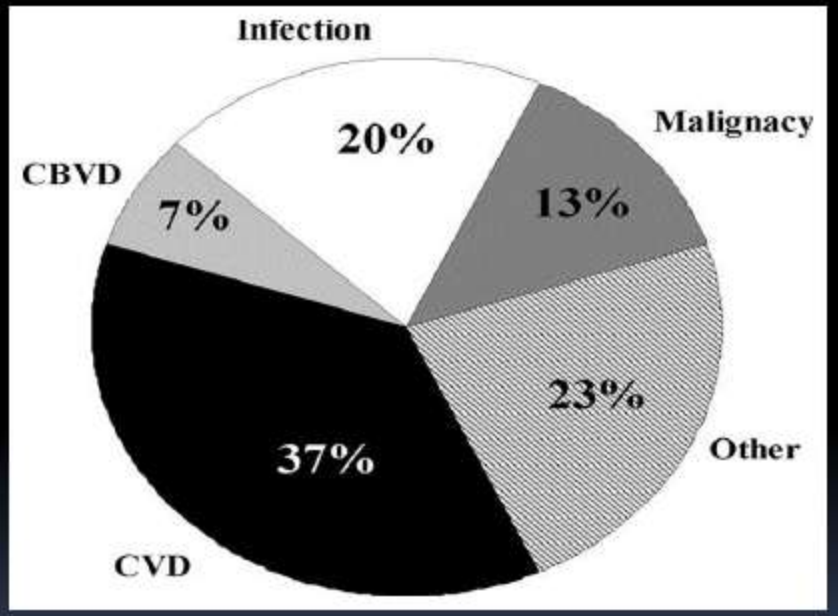
Impact of Hypertension on Graft Survival

Hypertension and Graft survival



Association of hypertension at 1 year with transplant survival. Kidney transplant survival is inversely proportional to blood pressure

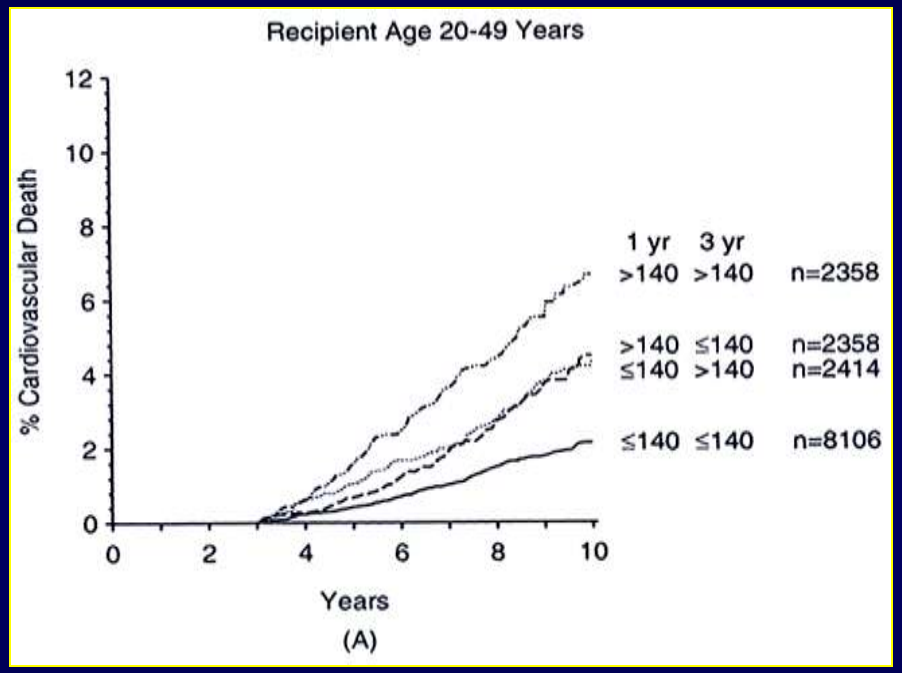
Mortality after kidney transplant

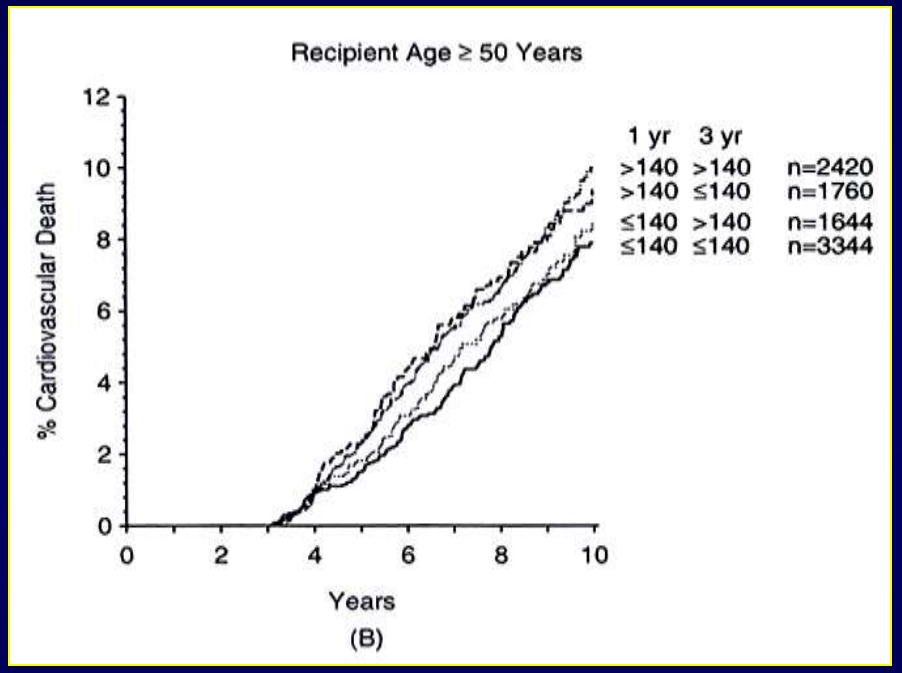


Atherosclerotic disease is the most common cause of death after transplant (44%) and outweighs the contributions from infection and malignancy combined (33%)

Mahendra M, John PV. Hypertension After Kidney Transplant. ***American Journal of Kidney Diseases.*** *2011 Feb; 57(2):331-341*

Rates of CARDIOVASCULAR DEATH in younger (A) or older (B) recipients depending on BP profiles at 1 and 3 years posttransplant





(Oplez et al., 2005)

American Journal of Transplantation 2005; 5: 2725–2731
Blackwell Munksgaard

doi: 10.1111/j.1600-6143.2005.01093.x

Improved Long-Term Outcomes After Renal Transplantation Associated with Blood Pressure Control

Gerhard Opelz* and Bernd Döhler for the Collaborative Transplant Study

Department of Transplantation Immunology, Institute of Immunology, University of Heidelberg, Germany
** Corresponding author: Gerhard Opelz, gerhard.opelz@med.uni-heidelberg.de*

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Management of Posttransplant Hypertension

CCBs:

- **Effectively counteract the afferent arteriolar vasoconstriction caused by CNI, a suggested mechanism for progressive allograft dysfunction.**
- **Use of CCBs + CyA → reduction in both DGF and acute rejection episodes, and possibly also a better long-term graft function.**

(Cosio F.G. et al., 2001)

- **Have a significant nephroprotective effect independent of the agent's antihypertensive actions.**

(Midvedt et al., 2001)

- **CCBs are relatively well tolerated.**
- **Concurrent administration of CNI and both nondihydropyridine (eg, verapamil and diltiazem) and dihydropyridine (eg, nifedipine, amlodipine, and isradipine) CCBs → drug interaction → ↑ CNI level.**

ACEIs and ARBs:

- known to slow down the progression of chronic renal disease.

Possible mechanism:

1. Decrease in intracapillary pressure.
2. A reduction in permselectivity.
3. Alterations in the function of the mesangial cells.
4. Interference with angiotensin-mediated generation of free radical formation.
5. Both ACEIs and ARBs may inhibit the activation of transforming growth factor-β1 (TGF-β1) (cytokine involved in the pathogenesis of chronic allograft dysfunction upregulated by intrarenal RAS and by direct effect of CyA).

- However, the ability of ACELs or ARBs to slow the progression of chronic allograft dysfunction still remains upproven. *(Yamada K. et al., 2003)*

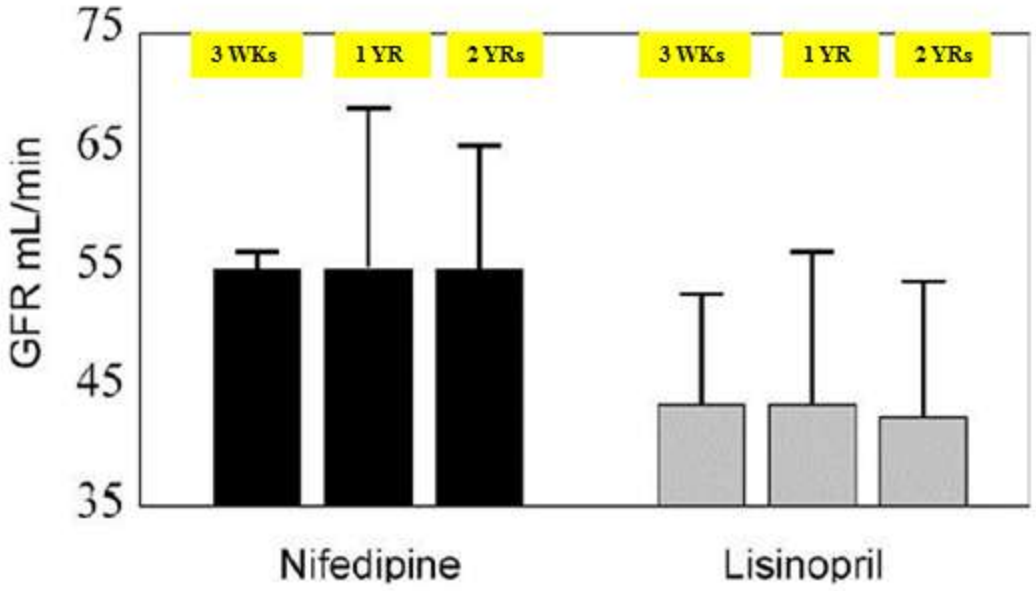
- **The administration of ACEIs and ARBs has been considered safe during *the later course of kidney transplantation* but, exacerbate acute renal failure and DGF when used early after transplantation in the presence of high doses of CNI.**
- **The blockade of the RAS may have beneficial effects on posttransplant kidney function because there is evidence that excess RAS activity in both the kidney donor and recipient are important contributors to the pathogenesis of DGF.** ***(Blumenfeld J.D. et al., 2001)***

✓ **Meta-analysis of randomized double-blind studies determined that they reverse LVH to a significantly greater degree than do β-blockers or diuretics. (*Klingbeil A.U. et al., 2003)***

✓ ***Losartan was more effective* in the prevention of cardiovascular morbidity and death than atenolol for a similar reduction in B** ***(Dahlöf B. et al., 2002)***

KIDNEY FUNCTION AND CHOICE OF ANTIHYPERTENSIVE AGENTS

GFR in patients treated with calcium channel blockers is greater than for those treated with ACEi



Hypertension After Kidney Transplant

Mahendra Mangray, MD, and John P. Vella, MD, FRCP

Am J Kidney Dis. 57(2):331-341.

KDOQI Guidelines 2013

Table 120. Stages and Clinical Features of Diseases in the Kidney Transplant Recipient

Stage Description	Clinical Features: Chronic Allograft Nephropathy	Drug Toxicity	Recurrent Disease	Transplant Glomerular Disease
At Increased Risk	All	Treatment with cyclosporine or tacrolimus	Glomerular diseases in native kidneys	All
Stage 1–2 Kidney Damage	HBP	HBP	Proteinuria	Proteinuria, HBP
Stage 3–4 Decreased GFR	HBP, Complications	HBP, Complications	HBP, Complications	HBP, Complications
Stage 5 Kidney Failure	Uremia, CVD	Uremia, CVD	Uremia, CVD	Uremia, CVD

Abbreviations: HBP, high blood pressure; CVD, cardiovascular disease

National Kidney Foundation®

KDOQI Guidelines 2013:

Table 121. Kidney Transplant Recipients: Selection of Antihypertensive Agents

Author, Year	N	Applicability	*Baseline			Comparators and Mean BP at end of study (mm Hg)		Clinical Outcomes				Methodological Quality
			GFR or Ccr (mL/min/1.73 m²) or S Creat (mg/dL)	Proteinuria (mg/24hr) ^denotes Albuminuria	Mean BP (mmHg)	Comparator 1	Comparator 2	Kidney Disease Progression	Proteinuria	CVD and Mortality	LVH	
ACE-I vs. Placebo												
Hernandez 2000 [488]	52	†††	Scr 1.5 (SD 0.07)	ND	148/90	Lisinopril 141/85	Placebo 151/91				+	●
ACE-I vs. BB												
Hausberg 1999 [484]	70	††	Ccr 85 (SD 8)	53^ (SD 12)	148/96	Quinipril 144/87	Atenolol 141/84	NS				●
ACE-I vs. Dihydropyridine CCB												
Midtvedt K 2001 [482]	154	†††	GFR 43 (SD 14)	129 (SD 270)	170/104	Lisinopril 140/85	Nifedipine 137/85	—				●
Mourad 1993 [483]	31	††	GFR 59 (SD 4)	118^ (SD 48)	161/98	Lisinopril ↓18 ± 3 (MAP change)	Nifedipine ↓13 ± 5 (MAP change)	NS				○
CCB vs. Placebo												
Rahn KH 1999 [486]	253	††	Scr 1.6 (SD 0.04)	ND	144/88	Nitrendipine 138/86	Placebo 143/90	+				●
van Riemsdijk 2000 [485]	210	††	Ccr 56	ND	ND	Isradipine ND	Placebo ND	+				○
Madsen JK 1998 [487]	99	†††	GFR 42 (SD 16)	ND	151/93	Felodipine 131/78	Placebo 144/84	+				○

Annotations of summary tables:

Footnotes:

* = baseline data from comparator 1 group are reported

^ = denotes albuminuria

Effect of Angiotensin II Receptor Blocker on Plasma Levels of TGF-β1 and Interstitial Fibrosis in Hypertensive Kidney Transplant Patients

Amgad E. El-Agroudy Nabil A. Hassan Mohamed A. Foda Amani M. Ismail
Essam A. El-Sawy Omar Mousa Mohamed A. Ghoneim

Urology and Nephrology Center, Mansoura University, Mansoura, Egypt

Am J Nephrol 2003;23:300–306

ELSEVIER

Renoprotective Effect of Early Inhibition of the Renin-Angiotensin System in Renal Transplant Recipients

D. Montanaro, M. Gropuzzo, P. Tulissi, C. Vallone, G. Boscutti, R. Mioni, A. Risaliti, U. Baccarani, G.L. Adani, M. Sainz, F. Bresadola, and G. Mioni

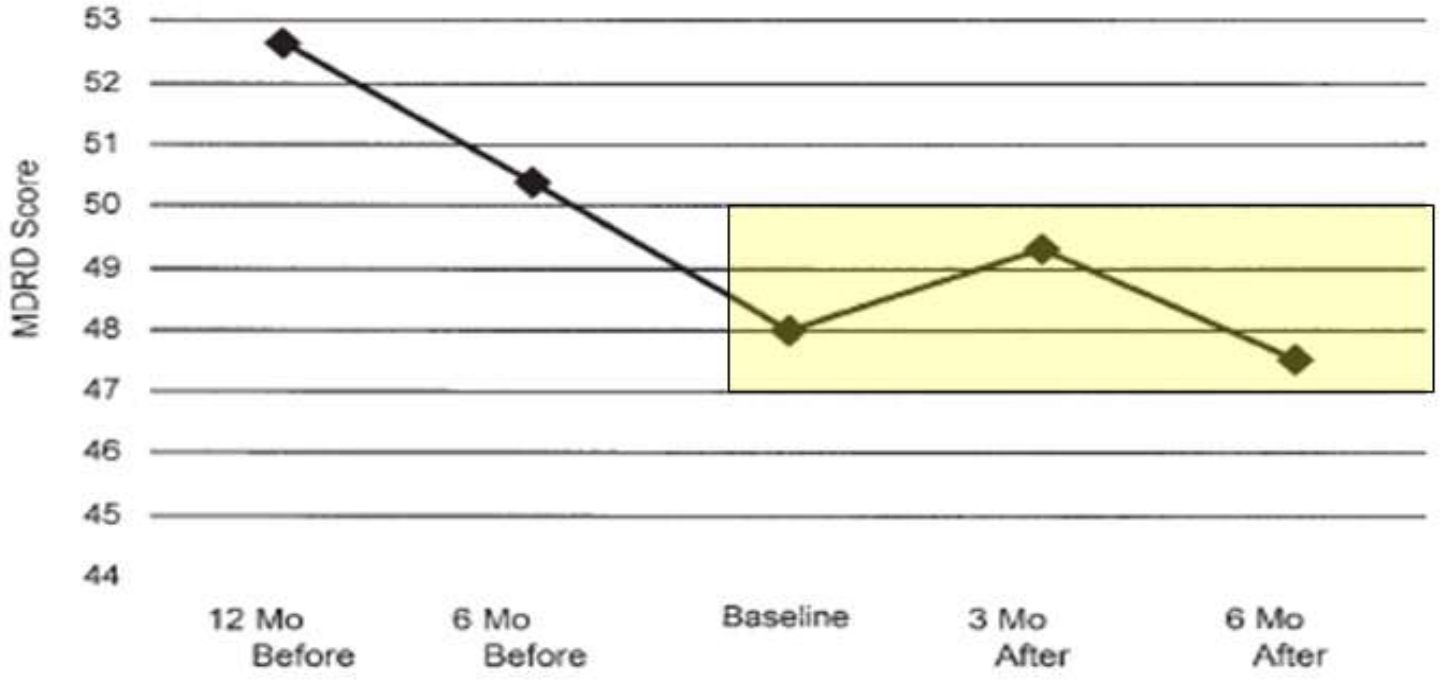
- **ACEI/ARB have renoprotective effects when used in patients with good stable renal function and mild proteinuria.**
- **May play a role to prevent chronic allograft nephropathy.**

ELSEVIER

Renin-Angiotensin System Dual Blockade Using Angiotensin Receptor Plus Aliskiren Decreases Severe Proteinuria in Kidney Transplant Recipients

V. López, M. Martin, C. Cobelo, P. Aranda, M. Cabello, E. Sola, C. Gutierrez, D. Burgos, D. Martínez, and D. Hernandez

Changes in renal function *from 12 months before to 6 months after initiation of* AliskirenTherapy.



Transplantation Proceedings, 42, 2883–2885 (2010)

N Engl J Med. 2005 Feb 10;352(6):558-69.

Angiotensin II type 1-receptor activating antibodies in renal-allograft rejection.

8 Slow, Difficult Steps To Become A Millionaire (The Daily Western)

Dragun D[1], Müller DN, Bräsen JH, Fritsche L, Nieminen-Kelhä M, Dechend R, Kintscher U, Rudolph B, Hoebeke J, Eckert D, Mazak I, Plehm R, Schönemann C, Unger T, Budde K, Neumayer HH, Luft FC, Wallukat G.

- 33 kidney-transplant recipients who had refractory vascular rejection.
- 13 had donor-specific anti-HLA antibodies,
- 20 did not. Malignant hypertension was present in 16 of the patients without anti-HLA antibodies, 4 of whom had seizures.

- Activating IgG antibodies targeting the AT1 receptor were detected in serum.
- The AT1 antagonist losartan blocked agonistic AT1-receptor antibody-mediated effects, and passive antibody transfer induced vasculopathy and hypertension in a rat kidney-transplantation model.

CONCLUSIONS:

A non-HLA, AT1-receptor-mediated pathway may contribute to refractory vascular rejection, and affected patients might benefit from removal of AT1-receptor antibodies or from pharmacologic blockade of AT1 receptors.

Chronic Allograft Nephropathy

ACEi, ARBs

- Slow down the progression of chronic allograft injury in experimental models

(Lutz et al., Kidney Int, 2006)

- Better than calcium channel blockers in protection against ch. Allograft injury.

(Amuchastegui et al JASN, 1998)

- ↓ TGF-b1 production (due to RAS inhibition)⟶ ↓ ch. allograft injury

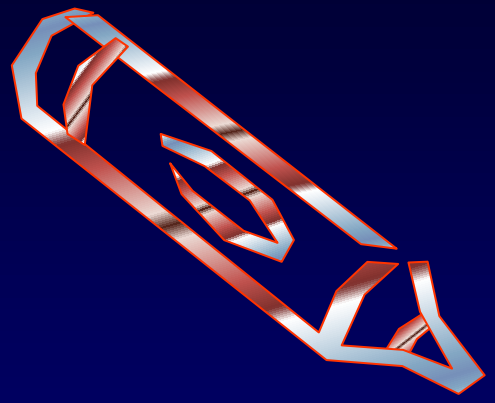
(*El Agroudy et al, Am J Nephrol, 2003)*

- RAS blockade →prevent or slow down progression of chronic renal damage …????

(Cruzado et al, Transpl Int, 2008)

B-BLOCKERS:

1. **Reduce morbidity and mortality after myocardial infarction.**
2. **Are also of benefit in the management of heart failure not only in the general population but also in patients with kidney disease.**
3. **Could be considered as a possible first-line therapy for posttransplant hypertension in patients with concomitant coronary heart disease.**
4. **Have an adverse lipid profile (increase triglyceride levels and ↓ HDL).**
5. **Have been associated with increased risk for new-onset diabetes mellitus.**
6. **Have potential limitation in patients receiving CNI, Target of Rapamycin (TOR) inhibitors, and/or corticosteroids. *(Hyperlipidemia)***
7. **Newer third-generation β-blockers (eg, carvedilol) have been shown to have a neutral or positive effect on dyslipidemia and insulin resistance.**



Summary

- **Arterial hypertension plays a major role in the progression to chronic allograft failure and in morbidity and mortality associated with CVD.**

- **Its prevalence varies with the type of immunosuppressive regimen, time after transplantation, and other interacting factors.**

- **Steroid-sparing protocols/ CNI sparing protocols have been shown to improve BP control and reduce cardiovascular risk factors, with low rates of allograft rejection and graft loss (particularly with concomitant use of low dose CNI + TOR inhibitors).**

- **The available data do not support the recommendation of any class of antihypertensive medications as preferred agents for long-term therapy to slow down the progression of kidney disease. CCB, ACEI, and ARB, diuretics, and β-blockers continue to have a role.**

- **Despite the concerns of risk for acute renal failure, hyperkalemia, and posttransplant anemia, ACEIs and ARBs are now considered valuable drugs for the transplant population. However, the ability of ACEIs or ARBs to slow the progression of chronic allograft dysfunction remains unproven at the present time.**


Thank you